# CLINICAL STUDY REPORT SYNOPSIS

**Sponsor:** Pfizer, Inc.

**Investigational Product:** Tanezumab/PF-04383119

**Clinical Study Report Synopsis:** Protocol A4091063

**Protocol Title:** A Phase 3 Randomized, Double-Blind, Active-Controlled, Multicenter Study of the Long-Term Safety and Efficacy of Subcutaneous Administration of Tanezumab in Japanese Adult Subjects With Chronic Low Back Pain

**Investigators:** Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

**Study Center(s):** A total of 58 sites randomized patients in this study. The study was conducted at sites in Japan.

**Publications Based on the Study:** None

**Study Initiation Date:** 26 May 2016

**Study Completion Date:** 11 June 2019

**Report Date:** 08 July 2020

**Previous Report Date(s):** 20 November 2019

**Phase of Development:** Phase 3

**Study Objectives**

**Primary Objective**

- To evaluate the long-term safety of tanezumab 5 mg and tanezumab 10 mg subcutaneously (SC) administrated every 8 weeks (7 administrations).

**Secondary Objective**

- To demonstrate the long-term analgesic efficacy of tanezumab 5 mg and tanezumab 10 mg SC administered every 8 weeks (7 administrations).

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## METHODS

### Study Design

This was a randomized, double-blind, active-controlled, multicenter, parallel-group, Phase 3 study of the safety and efficacy of tanezumab when administered by SC injection for up to 56 weeks in patients with chronic low back pain (CLBP). Patients were randomized to one of three treatment groups in a 1:1:1 ratio. Treatment groups included:

1. Placebo matching tanezumab SC administered at 8-week intervals (up to 7 doses) plus celecoxib 100 mg administered orally two times a day (BID) for 56 weeks.

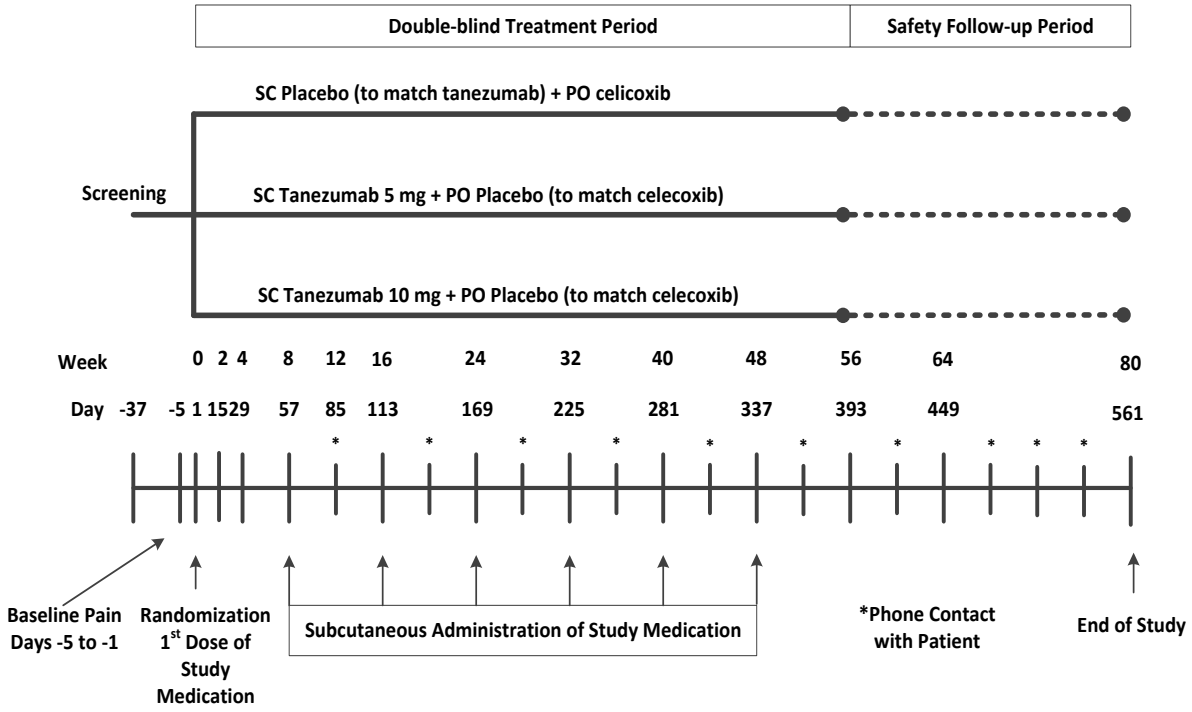
2. Tanezumab 5 mg SC administered at 8-week intervals (up to 7 doses) plus placebo matching celecoxib administered orally BID for 56 weeks.

3. Tanezumab 10 mg SC administered at 8-week intervals (up to 7 doses) plus placebo matching celecoxib administered orally BID for 56 weeks.

The Double-blind Treatment period began with the Baseline (Day 1) visit and concluded with completion of the Week 56 visit procedures.

The study was designed with a total duration (post randomization) of up to 80 weeks including the 24-week Safety Follow-up Period.

**Figure 1. Study Schematic**



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### Diagnosis and Main Criteria for Inclusion

- Japanese males or females, ≥18 years of age.

- Duration of CLBP for ≥3 months, and treatment with agents for low back pain (LBP) for ≥3 months. Primary location of LBP must have been between the 12$^{th}$ thoracic vertebra and the lower gluteal folds, with or without radiation into the posterior thigh, classified as Category 1 or 2 according to the classification of the Quebec Task Force in Spinal Disorders.

- Patients must have experienced some benefit from their current stable dose regimen of oral therapy of non-steroidal anti-inflammatory drug (NSAID) (celecoxib 200 mg/day [100 mg BID], loxoprofen 120 to 180 mg/day, or meloxicam 5 to 15 mg/day) treatment, have tolerated their NSAID regimen, have taken this medication regularly (defined as an average of at least five days per week) during the 30-day period prior to the Screening Visit and must have had some improvement in low back pain, but still require additional pain relief at Screening.

- Patients must have maintained a stable dose regimen of celecoxib 100 mg BID with a minimum compliance of 70% (ie, five of seven days per week) for at least the final two weeks (patients who were receiving celecoxib as pre-study treatment) or three weeks (patients who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening Period immediately prior to the Baseline (Day 1) visit.

- Patients must have had Low Back Pain Intensity (LBPI) score of ≥5 at Screening.

- Patients must have completed at least 4 daily pain diaries during the 5 days prior to the day of Randomization, with an average LBPI score of ≥5 and Patient's Global Assessment of Low Back Pain (PGA-LBP) must have been 'Fair', 'Poor' or 'Very Poor' at Baseline.

- Patients must have been willing to discontinue all pain medications for CLBP except rescue medication and study medication and not use prohibited pain medications for the duration of the study.

- Female patients of childbearing potential and at risk for pregnancy must have agreed to comply with protocol-specified contraceptive requirements.

- Female patients not of childbearing potential must have either: had a documented total hysterectomy and/or bilateral oophorectomy; had medically confirmed ovarian failure; or achieved postmenopausal status.

### Diagnosis and Main Criteria for Exclusion

- Body Mass Index (BMI) of >39 kg/m$^2$.

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- Diagnosis of osteoarthritis (OA) of the knee or hip as defined by the American College of Rheumatology (ACR) combined clinical and radiographic criteria. Radiographic criteria were assessed by the Central Reader:
    - Patients who had Kellgren-Lawrence (KL) grade ≥2 radiographic evidence of hip OA or KL grade ≥3 radiographic evidence of knee OA were excluded.
    - Patients who had KL grade ≤2 radiographic evidence of knee OA but did not meet ACR criteria and did not have pain associated with their knee OA were allowed.
- Patients with symptoms and radiologic findings (ie, joint space narrowing, osteophytes) consistent with OA in the shoulder.
- History of lumbosacral radiculopathy within the past two years, history of spinal stenosis associated with neurological impairment, or history of neurogenic claudication.
- Back pain due to recent major trauma (eg, vertebral fracture, post-traumatic spondylolisthesis) within six months prior to Screening.
- Surgical intervention including, but not limited to, procedures such as discectomy, nerve ablation, kyphoplasty, or nucleoplasty, during the past six months for the treatment of low back pain.
- Planned surgical procedure during the duration of the study.
- Fibromyalgia, back pain due to a visceral disorder (eg, endometriosis), or other moderate-to-severe pain that could have confounded assessments or self-evaluation of the pain associated with chronic low back pain.
- History of disease that could have involved the spine, including inflammatory joint diseases such as seronegative spondyloarthropathy (eg, ankylosing spondylitis), rheumatoid arthritis, infections or tumors of the spinal cord, or Paget's disease of the spine, pelvis, or femur.
- Radiographic evidence of any of the following conditions in any screening radiograph as determined by the Central Radiology Reviewer and as defined in the tanezumab program imaging atlas: excessive malalignment of the knee; severe chondrocalcinosis; other arthropathies (eg, rheumatoid arthritis); systemic metabolic bone disease (eg, pseudogout, Paget's disease, metastatic calcifications); large cystic lesions; primary or metastatic tumor lesions; or stress or traumatic fracture.
- Patients with radiographic evidence of any one of the following conditions as determined by the Central Radiology Reviewer and as defined in the tanezumab program imaging atlas at Screening: 1) Rapidly progressive OA, 2) Atrophic or Hypotrophic OA,

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3) Subchondral insufficiency fracture, 4) Spontaneous osteonecrosis of the knee, 5) Osteonecrosis, or 6) Pathologic fracture.

- Patients with a history of osteonecrosis or osteoporotic fracture (ie, a patient with a history of osteoporosis and a minimally traumatic or atraumatic fracture).

- History of significant trauma or surgery to a knee, hip, or shoulder within the previous year.

- Patients with a past history of carpal tunnel syndrome (CTS) with signs or symptoms of CTS in the one year prior to Screening.

- Patient considered unfit for surgery, defined as a Grade >3 on the American Society of Anesthesiologists (ASA) physical classification system for surgery or patients who would not be prepared to undergo joint replacement surgery if required.

- History of intolerance or hypersensitivity to the relevant oral celecoxib the patient could have been randomized to receive, or any of its excipients, or existence of a medical condition, or use of concomitant medication for which the use of celecoxib is contraindicated (refer to product labeling).

- History of intolerance or hypersensitivity to acetaminophen (paracetamol) or any of its excipients or existence of a medical condition or use of concomitant medication for which the use of acetaminophen/paracetamol was contraindicated (refer to product labelling).

- Use of prohibited medications or prohibited non-pharmacological treatments without the appropriate washout period (if applicable) prior to Screening or Initial Pain Assessment Period (IPAP).

- History of known alcohol, analgesic, or narcotic abuse within two years of Screening.

- Presence of drugs of abuse (including prescription medications without a valid prescription) or illegal drugs in the urine toxicology screen obtained at Screening.

- History of allergic or anaphylactic reaction to a therapeutic or diagnostic monoclonal antibody or IgG-fusion protein.

- Signs and symptoms of clinically significant cardiac disease.

- Resting, sitting blood pressure (BP) ≥160 mm Hg in systolic pressure or ≥100 mm Hg in diastolic pressure at Screening. If a patient was found to have untreated significant hypertension at Screening and antihypertensive treatment was initiated, assessment for study eligibility was deferred until BP and antihypertensive medication were stable for at

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least one month. For patients with previously diagnosed hypertension, antihypertensive medications must have been stable for at least one month prior to Screening.

- Patients who had evidence of orthostatic hypotension (OH) based upon replicate orthostatic BP measurements. If the orthostatic BP change could not be determined (eg, unable to establish a stable supine systolic and diastolic BP), then the patient was not eligible for the study.

- Patients with a total impact score of >7 on the Survey of Autonomic Symptoms (SAS).

- Diagnosis of a transient ischemic attack in the six months prior to Screening, diagnosis of stroke with residual deficits (eg, aphasia, substantial motor or sensory deficits) that could preclude completion of required study activities.

- Patient was expected to undergo a therapeutic procedure or to use any analgesic other than those specified in the protocol during the pre-treatment and treatment periods that was likely to confound assessment of analgesic efficacy or safety.

- Previous exposure to exogenous nerve growth factor (NGF) or to an anti-NGF antibody.

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3.0 times the upper limit of normal (ULN), or creatinine exceeding 1.7 mg/dL (150 µmol/L) in men or 1.5 mg/dL (133 µmol/L) in women, or hemoglobin (Hb) A1c ≥10% at Screening. Repeat confirmatory tests could be performed.

- Positive Hepatitis B, Hepatitis C virus (HCV), or human immunodeficiency virus (HIV) tests at screening indicative of current infection.

- History, diagnosis, or signs and symptoms of clinically significant neurological disease or clinically significant psychiatric disorder.

- Pregnant female patients; breastfeeding female patients; female patients of childbearing potential who were unwilling or unable to use two highly effective methods of contraception for the duration of the study and for 112 days (16 weeks) after the last dose of study medication.

- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that could have increased the risk associated with study participation or study medication administration or could have interfered with the interpretation of study results and, in the judgment of the Investigator, could have made the patient inappropriate for entry into this study.

- Participation in other studies involving investigational drug(s) (Phase 1-4) within 30 days (90 days for biologics) before Screening and/or during study participation.

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### Randomization Criteria

- Patient must have completed appropriate washout of analgesics.
- Patients must have entered at least four LBPI scores on the daily pain diary in the five days prior to the Baseline (Day 1) visit.
- Patients must have maintained a stabilized dose regimen of celecoxib 100 mg BID with a minimum compliance of 70% (ie, five of seven days per week) for at least the final two weeks (patients who were receiving celecoxib as pre-study treatment) or three weeks (patients who were receiving loxoprofen or meloxicam as pre-study treatment) of the Screening period directly prior to the Baseline (Day 1) visit.
- Patients must have abstained from taking rescue medication (acetaminophen/ paracetamol) in the 24 hours that preceded dosing.
- Patients must have met the Baseline LBPI score and PGA-LBP Baseline requirements.
- Review of the electrocardiogram (ECG) and laboratory results and confirmation that there were no clinically significant or exclusionary findings.
- Radiographic eligibility must have been confirmed by the Central Reader.

### Study Treatment

Tanezumab, placebo for tanezumab, celecoxib, and placebo for celecoxib were supplied by the Sponsor or designee (Table S1).

Tanezumab 5 mg and tanezumab 10 mg were each presented as a sterile solution for SC administration, in a glass pre-filled syringe (PFS). Each PFS contained a sufficient amount of tanezumab to provide the intended dose of drug at a concentration of 5 mg/mL or 10 mg/mL. Each PFS was packed in an individual carton and had a unique container number.

Placebo for tanezumab was presented as a sterile solution for SC administration in a matching glass PFS. Each PFS was packaged in an individual carton and had a unique container number.

Celecoxib was provided as oral capsules containing 100 mg of active celecoxib. Celecoxib 100 mg was packaged in high-density polyethylene (HDPE) bottles with child-resistant closures. The bottles used for the screening period contained 80 capsules (open-label supply) and the bottles used for the treatment period contained 70 capsules (Double-blind supply).

Placebo for celecoxib was provided as oral capsules matching those used for celecoxib 100 mg capsules. Placebo to match celecoxib 100 mg was packaged in HDPE bottles with child-resistant closures containing 70 capsules (Double-blind supply).

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**Table S1. Investigational Product Description**

| Investigational Product Description | Vendor Lot Number | Pfizer Lot Number | Strength/Potency | Dosage Form |
|---|---|---|---|---|
| PF-04383119 Solution for Injection, 5 mg/mL | L50447 | 15-002258 | 5 mg/mL | PFS |
| PF-04383119 Solution for Injection, 10 mg/mL | L52539 | 15-002260 | 10 mg/mL | PFS |
| Placebo for PF-04383119 Solution for Injection | L39168 | 15-002262 | 0 mg/mL | PFS |
| Celecoxib, 100 mg | T0173V | 12-004951 | 100 mg | Capsule |
| | H04083 | 13-111559 | 100 mg | |
| | S49797 | 17-000829 | 100 mg | |
| Placebo for 100 mg/200 mg Celecoxib | H04007 | 13-111563 | 0 mg | Capsule |
| | H04009 | 13-111564 | 0 mg | |
| | S49791 | 17-000830 | 0 mg | |

## EFFICACY EVALUATIONS

### Primary Endpoints

The primary endpoint in this study was safety.

### Secondary Endpoints

Questionnaires for efficacy parameters were completed by the patients at the site via the Interactive Response Technology (IRT) (electronic tablets), or at home via electronic diaries. Questionnaires at the site were completed prior to dosing on dosing days.

Efficacy endpoints included: Change from Baseline to Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, and 64 in average LBPI score as measured by an 11-point numeric rating scale (NRS); Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in the Roland-Morris Disability Questionnaire (RMDQ) total score; Change from Baseline to Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, and 64 in PGA-LBP; Cumulative distribution of percent change from Baseline in average LBPI score to Weeks 16, 24, and 56; Response as defined by a ≥30%, ≥50%, ≥70%, and ≥90% reduction from Baseline in weekly average LBPI score derived from the patient diary at Weeks 16, 24, 40, and 56; Change from Baseline to Weeks 2, 4, 8, 16, 24, 40, 56, and 64 in the Brief Pain Inventory short form (BPI-sf) scores for Worst Pain, Average Pain, Pain Interference Index (composite function score), Pain Interference with General Activity, Pain Interference with Walking Ability, Pain Interference with Sleep, and Pain Interference with Normal Work; CLBP Responder Index analysis (composite endpoint of average LBPI score, PGA-LBP, and RMDQ total score) at Weeks 16, 24, 40, and 56; Treatment Response: Improvement of ≥2 points in PGA-LBP at Weeks 16, 24, 40, and 56; Euro Quality of Life Health State Profile™ (EQ-5D-5L) dimensions and overall health utility score at Baseline, Weeks 16 and 56; Work Productivity and Activity Impairment Questionnaire: Low Back Pain (WPAI:LBP) change from Baseline to Week 16, 56, and 64, in the percent work time missed due to CLBP, percent impairment while working due to

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CLBP, percent overall work impairment due to CLBP, and percent activity impairment due to CLBP; Incidence of and time to discontinuation due to lack of efficacy; Usage of rescue medication (incidence, and number of days of usage) during Weeks 1, 2, 4, 8, 12, 16, 24, 32, 40, 48, 56, and 64; Usage of rescue medication (amount taken) during Weeks 1, 2, 4, 8, 12, and 16; and Health Care Resource Utilization (HCRU) at Baseline, Weeks 64, and 80.

Patient-reported outcome endpoints included Treatment Satisfaction Measures: Treatment Satisfaction Questionnaire for Medication v. II (TSQM) score at Weeks 16 and 56; and Patient Reported Treatment Impact Assessment-Modified (mPRTI) at Weeks 16 and 56.

### Pharmacokinetic and Pharmacodynamic Evaluations

Pharmacokinetic (PK) blood samples were collected at Baseline (Day 1; pre-dose) and at Weeks 2 and 4, Week 8 (pre-dose), Week 16 (pre-dose), Week 32 (pre-dose), Week 48 (pre-dose), Week 56, and Week 64. If participants terminated prior to Week 56, PK were determined at approximately 8 and 16 weeks after the last SC dose was administered. Tanezumab samples were assayed using a validated analytical method in compliance with Sponsor standard operating procedures.

Tanezumab concentrations were measured to support the development of an SC administration population PK model that allows for the prediction of the tanezumab concentration over time in individuals. In addition, tanezumab concentrations were measured to inform the immunogenicity profile of tanezumab.

Pharmacodynamic (PD) blood samples for the assessment of NGF (total NGF and proNGF) and soluble p75 were collected at Baseline (Day 1; pre-dose), at Weeks 2 and 4, Week 8 (pre-dose), Week 48 (pre-dose), and at Weeks 56 and 64 (or at Early Termination). Blood and urine samples for the assessment of biomarkers were collected at Baseline (Day 1; pre-dose).

## SAFETY EVALUATIONS

Safety evaluations for this study included assessment of adverse events (AEs); standard safety assessments (safety laboratory testing [chemistry and hematology], vital signs); orthostatic (supine/standing) BP assessments; SAS scores; ECG (12-lead) assessments; joint safety adjudication outcomes; total joint replacements (TJRs); neurologic examination (Neuropathy Impairment Score [NIS]); anti-drug antibody (ADA) assessments; and physical examinations.

### Safety Assessments

Adverse events (AEs), including serious adverse events (SAEs) and deaths, were collected throughout the study. A general physical examination was performed at Screening and at Week 56 or at Early Termination. Blood samples for clinical laboratory testing were collected at Screening, Baseline, Week 16, and Week 64, or at Early Termination Visit 2. For female patients of childbearing potential, serum pregnancy tests were conducted at

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Screening, Weeks 56 and 64, or at Early Termination Visits 1 and 2. Urine pregnancy tests were performed at Baseline (Day 1, predose), and predose at Weeks 8, 16, 24, 32, 40, and 48. Vital signs (including systolic and diastolic BP and pulse rate) were collected and recorded at Screening, Baseline, prior to SC dosing at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80, or at Early Termination. Vital signs were collected after the patient had been in a sitting position for at least five minutes at each visit. In addition to sitting vital sign measurements, orthostatic BP measurements were obtained using a standard manual sphygmomanometer at Screening, Baseline and at Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80, or at Early Termination. A 12-lead ECG was performed at Screening, Weeks 16, 56, and 80, and at Early Termination Visits 1 and 3 for determination of ECG-related eligibility and safety monitoring.

### Neurological

An AE of OH was reported for all patients meeting criteria for OH at a visit. If no apparent medical cause was identified at the time the OH criteria were met and the patient was symptomatic, the patient was further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible. If an apparent medical cause was identified at the time the OH criteria were met or if the patient was asymptomatic, the patient had a repeat assessment of OH performed at least one week, but not more than four weeks later. If confirmed OH was present at the follow-up visit, the patient was further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

Patients reporting AEs of any seriousness or severity with preferred terms of Bradycardia, Syncope, OH, Anhidrosis, or Hypohidrosis were further evaluated for the presence of sympathetic autonomic neuropathy by a cardiologist or neurologist as soon as possible.

Neurological examinations were performed at Screening, Baseline, and Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80, or at Early Termination; the NIS was completed at these time points based on this neurological examination. Neurologic examination assessed strength of groups of muscles of the head and neck, upper limbs and lower limbs, deep tendon reflexes, and sensation (tactile, vibration, joint position sense and pinprick) of index fingers and great toes to complete the NIS.

The SAS was completed by the patient at Screening, prior to SC dosing at Week 24, and at Weeks 56 and 80, or at Early Termination Visits 1 and 3.

A neurological evaluation was performed by a consulting neurologist if an AE suggestive of new or worsening peripheral neuropathy or an AE of abnormal peripheral sensation was reported as an SAE, resulted in the patient being withdrawn from the study, was ongoing at the end of the patient's participation in the study, or was of severe intensity. Neurological evaluations were also obtained if a new or worsened clinically significant abnormality on the neurologic exam was reported as an AE and met criteria listed above, or if a reported

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non-neuropathic neurological AE (eg, stroke, seizure) was considered medically important by the Investigator.

### Musculoskeletal and Joint-Related

Each patient underwent a musculoskeletal physical examination at Screening, Baseline, Weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 80, or Early Termination. A thorough musculoskeletal history was collected at Screening wherein the Investigator inquired about current and past history of OA, ligament tear or rupture, joint surgeries (including arthroscopic procedures), fractures, gout, osteoporosis or osteopenia, join injuries, or other conditions. At each subsequent visit, the Investigator conducted a thorough musculoskeletal physical examination of all major joints. This examination evaluated the joints for swelling, redness, tenderness, deformity, osteophytes or nodes, crepitus, and pain on motion. Findings were documented on the appropriate case report form. Information was also collected on any patient-reported joint symptoms including pain, stiffness, and swelling. Any clinically significant change in symptoms or the examination was reported as an AE.

Radiographic assessments (X-rays) of the hips, knees and shoulders were obtained at Screening, Weeks 24, 56, and 80, or at Early Termination Visits 1 and 3.

A central radiology reader reviewed the X-ray images for assessment of eligibility. During the study, the Central Reader reviewed X-ray images for continued radiologic eligibility and for diagnosis of joint conditions that would warrant further evaluation by the Adjudication Committee.

For patients who were identified with a possible or probable joint event (ie, Rapidly progressive OA, Subchondral insufficiency fracture, Primary osteonecrosis, or Pathological fracture) and patients undergoing TJR for any reason, all images and other source documentation were provided to the blinded Tanezumab Adjudication Committee for review and adjudication of the event. The Adjudication Committee's assessment of the event represented the final classification of the event.

### Immunogenicity

Blood samples for the assessment of ADA (anti-tanezumab antibodies) were collected at Baseline (Day 1; predose) and Weeks 8 (predose), 16 (predose), 32 (predose), 48 (predose), 56, 64, and 80. If patients terminated prior to Week 56, ADA was determined at approximately 8, 16, and 24 weeks after the last dose of SC study medication was administered or at Early Termination.

### Adverse Event Reporting

For SAEs, the active reporting period to Pfizer or its designated representative began from the time that the patient provided informed consent, which was obtained prior to the patient's participation in the study (ie, prior to undergoing any study-related procedure and/or receiving study medication) through the end of the Safety Follow-up Period or through and

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including 112 calendar days after the patient's last administration of the SC study medication, if the patient refused the protocol-defined Follow-up Period.

## STATISTICAL METHODS

A minimum sample size of approximately 130 patients per treatment group was needed for the safety evaluation. The total sample size was planned to be approximately 390 patients.

The primary objective of this study was to evaluate safety; the sample size was calculated to obtain approximately 100 Japanese CLBP patients per group (ie, 80 to 100 patients per group) with one year's exposure of tanezumab.

> **NOTE:** The planned sample size was reduced in Protocol Amendment 2. Considering study feasibility, the number of patients with one-year exposure and the capability of safety evaluation with the data from this study, the target sample size was changed to approximately 200 (170-220) patients. Additionally, from the safety perspective, it was acceptable to randomize more than 220 patients.

When approximately 170 patients were enrolled in this study, AEs related to abnormal peripheral sensation and decreased sympathetic function were expected to occur in several patients so neurological safety could be evaluated with high probability in Japanese patients.

### Analysis of the Primary (Safety) Endpoints

AEs, concomitant medications, laboratory safety tests, physical and neurological examinations, vital signs, ECG, and ADA were collected for each patient. Standard safety reporting tables summarized and listed the safety data.

AEs of Syncope, Bradycardia, OH, Anhidrosis, and Hypohidrosis were designated as AEs of interest that were reviewed by the unblinded External Data Monitoring Committee (E-DMC).

A three-tier AE reporting approach was used. A pre-specified composite AE of potential sympathetic dysfunction (Syncope, Bradycardia, OH, Anhidrosis, and Hypohidrosis) was considered clinically important and classified as a Tier 1 AE. Tier 2 AEs were those with a frequency of ≥3% in any treatment group. Tier 3 AEs were those not in Tier 1 or Tier 2. AEs within Tier 1 and Tier 2 were summarized using risk differences between each tanezumab group and celecoxib, together with 95% confidence interval (CI), using exact methods. There was no multiplicity adjustment for these significance tests.

### Analysis of Secondary (Efficacy) Endpoints

All efficacy analyses used the Intent-to-Treat (ITT) analysis set. If not otherwise specified, the observed data (no imputation for missing data) were summarized.

The descriptive statistics n, mean, median, standard deviation (SD), minimum (min), maximum (max), and 95% CI were used to summarize the endpoints. The analysis for change from Baseline of average LBPI used a mixed model analysis of covariance

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(ANCOVA) with a fixed effect of treatment group, Baseline average LBPI as a covariate, and study site as a random effect. The analysis for change from Baseline of RMDQ used a mixed model ANCOVA with a fixed effect of treatment group, Baseline score, and Baseline average LBPI as covariates, and study site as a random effect. Change from Baseline at each time point was estimated using LS means with SE and 95% CI. Estimates of treatment differences between each tanezumab treatment group versus celecoxib group was done using least squares (LS) means with standard error (SE) and 95% CI. P-values were not shown.

Missing LBPI, RMDQ, PG, and BPI-sf data were handled using a multiple imputation approach, with imputation dependent on the reason for missing data. Data missing due to treatment discontinuation due to death, AEs, insufficient clinical response, or patient's meeting protocol-specified pain criteria for discontinuation; used a multiple imputation version of a baseline observation carried forward (BOCF) single imputation method. Multiple imputations were created by sampling from a normal distribution based on the patient’s Baseline score and the SD (over all treatment groups) of the observed efficacy data at the timepoint over all ITT patients. Data missing due to other reasons used a multiple imputation version of a last observation carried forward (LOCF) single imputation method. Multiple imputations were created by sampling from a normal distribution based on the patient’s last score and the SD (over all treatment groups) of the observed efficacy data at the timepoint over all ITT patients.

### Analysis of Pharmacokinetic Data

Pharmacokinetic data were reported as follows:

- A listing of all plasma tanezumab concentrations sorted by patient, active treatment group, and nominal time post dose. The listing of concentrations includes the actual times post-dose.

- A descriptive summary of the plasma tanezumab concentrations based on nominal time post dose for each treatment group.

- Boxplots of tanezumab plasma trough concentrations at the nominal times for the tanezumab treatment groups.

### Pharmacodynamic Analysis

Serum samples were run in the bioanalytical assays for the assessment of NGF and the measurements were summarized in the following tables and figures:

- A listing of individual NGF concentrations sorted by patient, active treatment group, and time postdose.

- Descriptive statistics of NGF concentrations based on time postdose for each treatment group.

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- Box plots of NGF over time postdose for each treatment group.

## RESULTS

### Patient Disposition and Demography

Of 409 patients screened for entry the study, 277 patients were randomized to double-blind treatment and received study medication according to assigned treatment.

A summary of disposition events is shown in Table S2. Slightly more than half (53.4%) of all patients completed the Treatment Phase of the study; more patients in the tanezumab 5 mg treatment group (67.4%) than in the tanezumab 10 mg treatment group (46.2%) or the celecoxib treatment group (46.7%) completed the Treatment Phase. The most frequent reason for discontinuation during the Treatment Phase in any treatment group was due to meeting protocol-specified pain criteria for discontinuation; more patients discontinued for this reason in the tanezumab 10 mg treatment group (37.6%) and the celecoxib treatment group (38.0%) than in the tanezumab 5 mg treatment group (27.2%). The majority of patients (92.8%) completed the study; an approximately equal proportion of patients in the tanezumab 5 mg treatment group (95.7%) and the celecoxib treatment group (94.6%), and a smaller proportion in the tanezumab 10 mg treatment group (88.2%).

One patient entered the substudy.

**Table S2. Data Set Analyzed**

| | Tanezumab 5 mg (N=92) n (%) | Tanezumab 10 mg (N=93) n (%) | Celecoxib (N=92) n (%) | Total (N=277) n (%) |
|---|---|---|---|---|
| Screened: 409<br>Screen Failure: 130<br>Other Screened but not Randomized: 2 | | | | |
| Randomized | 92 (100.0) | 93 (100.0) | 92 (100.0) | 277 (100.0) |
| Treated | 92 (100.0) | 93 (100.0) | 92 (100.0) | 277 (100.0) |
| Not Treated | 0 | 0 | 0 | 0 |
| ITT Population | 92 (100.0) | 93 (100.0) | 92 (100.0) | 277 (100.0) |
| Safety Population | 92 (100.0) | 93 (100.0) | 92 (100.0) | 277 (100.0) |
| TJR (Total Joint Replacement) Subset Population | 0 | 1 (1.1) | 0 | 1 (0.4) |
| Completed study | 88 (95.7) | 82 (88.2) | 87 (94.6) | 257 (92.8) |
| Discontinued study | 4 (4.3) | 11 (11.8) | 5 (5.4) | 20 (7.2) |

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**Table S2. Data Set Analyzed**

| | Tanezumab 5 mg (N=92) n (%) | Tanezumab 10 mg (N=93) n (%) | Celecoxib (N=92) n (%) | Total (N=277) n (%) |
|---|---|---|---|---|
| Number of subjects[1] | | | | |
| Completed Treatment Phase | 62 (67.4) | 43 (46.2) | 43 (46.7) | 148 (53.4) |
| Completed Safety Follow-Up | 61 (66.3) | 42 (45.2) | 43 (46.7) | 146 (52.7) |
| Discontinued Safety Follow-Up | 1 (1.1) | 1 (1.1) | 0 | 2 (0.7) |
| Discontinued Treatment Phase | 30 (32.6) | 50 (53.8) | 49 (53.3) | 129 (46.6) |
| Completed Safety Follow-Up | 27 (29.3) | 40 (43.0) | 44 (47.8) | 111 (40.1) |
| Discontinued Safety Follow-Up | 2 (2.2) | 4 (4.3) | 2 (2.2) | 8 (2.9) |
| Did not enter Safety Follow-Up | 1 (1.1) | 6 (6.5) | 3 (3.3) | 10 (3.6) |
| Entered into Sub-Study | 0 | 1 (1.1) | 0 | 1 (0.4) |

N is Number of Subjects Randomized. Percentages are based on the number of subjects Randomized.
[1]Subjects in Safety Population.
Not treated is subjects who received no SC study medication.
Safety population consists of all subjects treated with Tanezumab or Placebo SC. ITT population consists of all randomized subjects who received at least one dose of
Tanezumab or Placebo SC.
"Other Screened but not Randomized" displays subjects who were screened but not randomized for a reason not related to a specific eligibility criterion.
CCI [redacted]

Demographic characteristics were similar across the treatment groups. The mean age and age range were similar across treatment groups which were overall balanced within each age category. There were more male than female patients in the tanezumab 5 mg treatment group (59.8% male) and the celecoxib treatment group (58.7% male), while the tanezumab 10 mg treatment group (52.7% male) was more balanced. All patients were randomized at sites in Japan and all patients were Asian (Japanese). The mean height, weight, and BMI were similar across treatment groups. Over 90% of patients across treatment groups had not been diagnosed with diabetes mellitus.

Inclusion criteria required that patients have experienced some benefit from their current stable dose regimen of oral therapy of NSAID (celecoxib, loxoprofen, or meloxicam). These were the prior drug treatments for CLBP identified as meeting inclusion criteria and may not include all prior medications for CLBP. There was no limit on the recall period for these prior treatments for CLBP. Of these protocol-qualifying drugs, across all treatment groups, celecoxib was the most frequently used drug treatment prior to study entry, followed by loxoprofen; meloxicam was used by 2 patients overall.

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The mean duration since diagnosis of LBP ranged from 7.7 to 9.1 years across treatment groups. Baseline disease characteristics such as average LBPI score, mean RMDQ Total Score, PGA-LBP, and BPI-sf scores were similar across the treatment groups. The Quebec Task Force Classification was similar across treatment groups, with most patients in Quebec Task Force Category 1 (pain without radiation) at Baseline. In the painDetect evaluation, most patients did not have a neuropathic component of their CLBP (painDetect score ≤12). The tanezumab 5 mg treatment group had a higher proportion of patients in the painDetect ≥19 category (neuropathic component is likely) and a smaller proportion in the 13 to 18 (neuropathic component uncertain) category compared to the other treatment groups, while the tanezumab 10 mg treatment group had a higher proportion of patients in the 13 to 18 category and a smaller proportion in the ≥19 category compared to the other treatment groups.

The proportion of patients assessed as having pain due to degenerative disc disease was 34.8%-43.0%. CLBP due to degenerative joint disease/OA was assessed in 11.8%-18.5% of patients across treatment groups. The remainder of patients (39.1%-51.1%) had pain due to Other/Injury/Muscle strain.

### Efficacy Results

The study was not designed or powered to detect treatment differences between the tanezumab and celecoxib treatment groups; there were no formal hypotheses to be tested for the efficacy endpoints.

### Primary Efficacy Analysis

The primary endpoints in this study were safety; refer to the Safety Results section.

### Secondary Efficacy Analysis

- Starting at Week 4 in the tanezumab 5 mg treatment group and at Week 1 in the tanezumab 10 mg treatment group and continuing through Week 64, patients in the tanezumab treatment groups showed a larger **change from Baseline in the mean LBPI score** (decrease = improvement) than those in the celecoxib treatment group (Observed Data). The tanezumab 5 mg treatment group showed larger LS mean changes from Baseline in the mean LBPI score than those in the tanezumab 10 mg treatment group from Week 16 though Week 56 and the celecoxib treatment group starting at Week 4 through Week 56. The tanezumab 10 mg treatment group showed a larger LS mean change from Baseline in the mean LBPI score than the celecoxib treatment group starting at Week 2 through Week 48; at Week 56 the LS mean change from Baseline in patients in the tanezumab 10 mg treatment group was similar to those in the celecoxib treatment group (Multiple Imputation).

- Starting at Week 2 and continuing through Week 56, patients in the tanezumab treatment groups, except at Week 24 in the tanezumab 5 mg treatment group, showed a larger **change from Baseline in the mean RMDQ score** (decrease=improvement) than those in

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the celecoxib treatment group (Observed Data). Patients in the tanezumab 5 mg treatment group showed a larger decrease in the LS mean change from Baseline in the RMDQ score than those in the tanezumab 10 mg treatment group at Week 32 through Week 56. The LS mean change from Baseline (decrease = improvement) in patients in the tanezumab 5 mg treatment group was larger than those in the celecoxib treatment group at Weeks 2 and 4, and at Week 24 through Week 56; at Weeks 8 and 16, the LS mean change from Baseline between the tanezumab 5 mg treatment group and the celecoxib treatment group was similar. Patients in the tanezumab 10 mg treatment group showed a larger LS mean change (decrease) from Baseline in the RMDQ score than those in the celecoxib treatment group starting at Week 2 through Week 24; starting at Week 32 and continuing through Week 56, the LS mean change from Baseline in patients in the tanezumab 10 mg treatment group was similar to those in the celecoxib treatment group (Multiple Imputation).

- Starting at Week 2 and continuing through Week 56 patients in the tanezumab 5 mg treatment group showed a larger **change from Baseline in the mean PGA-LBP score** (decrease = improvement) compared to patients in the celecoxib treatment group. Starting at Week 2 and continuing through Week 8, and at Weeks 24 and 32, patients in the tanezumab 10 mg treatment group showed a larger decrease from Baseline in the mean PGA-LBP compared to patients in the celecoxib treatment group (Observed Data). At Week 16 and Week 56, patients in the tanezumab 5 mg treatment group showed a larger decrease from Baseline in the mean PGA-LBP score than those in the tanezumab 10 mg treatment group and the celecoxib treatment group; the mean PGA-LBP scores for patients in the tanezumab 10 mg treatment group were similar to those for patients in the celecoxib treatment group (Multiple Imputation).

- At Week 16, there was a higher percentage of patients in the tanezumab 5 mg treatment group than in the celecoxib treatment group with a cumulative **reduction from Baseline in the average LBPI score** of >0% to ≥80%; in the tanezumab 10 mg treatment group, a higher percentage of patients showed a cumulative ≥60% to ≥80% reduction from Baseline in the average LBPI score than in the celecoxib treatment group (Mixed BOCF/LOCF).

  At Week 24, there was a higher percentage of patients in the tanezumab 5 mg treatment group with >0% to ≥50% **cumulative reduction from Baseline in the average LBPI score** than in the tanezumab 10 mg treatment group and a >0% to ≥90% cumulative reduction from Baseline in the average LBPI score than in the celecoxib treatment group; in the tanezumab 10 mg treatment group, a higher percentage of patients showed a ≥50% to ≥80% cumulative reduction from Baseline in the average LBPI score than in the celecoxib treatment group (Mixed BOCF/LOCF).

  At Week 56, there was a higher percentage of patients in the tanezumab 5 mg treatment group with a >0% to ≥90% **cumulative reduction from Baseline in the average LBPI score** than in the tanezumab 10 mg treatment group and the celecoxib treatment group.

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Only at the ≥70% response level was there a higher percentage of patients in the tanezumab 10 mg treatment group than in the celecoxib treatment group showing a cumulative reduction from Baseline in the average LBPI score; at all other response levels, percentage of patients in the tanezumab 10 mg treatment group was similar to that in the celecoxib treatment group.

- Treatment with tanezumab 5 mg was associated with a higher percentage of responders with a **reduction from Baseline in the weekly average LBPI score** compared to tanezumab 10 mg treatment at the ≥30% and ≥50% levels at each timepoint measured (Weeks 16, 24, 40, and 56), for a ≥70% reduction from Baseline at Weeks 40 and 56, and for a ≥90% reduction from Baseline at Week 56. Treatment with tanezumab 5 mg was associated with a higher percentage of responders compared to celecoxib treatment for all response levels (≥30%, ≥50%, ≥70%, ≥90% reduction from Baseline) at each timepoint measured, except for a ≥90% reduction from Baseline at Week 16. Treatment with tanezumab 10 mg was associated with a higher percentage of responders compared to celecoxib treatment for a ≥50% reduction from Baseline at Weeks 24 and 40; for a ≥70% reduction from Baseline at Weeks 16, 24, 40, and 56; and for a ≥90% reduction from Baseline at Week 40.

  Overall, the percentage of responders with a **reduction from Baseline in the weekly average LBPI score** in the tanezumab treatment groups was either comparable to or greater than those in the celecoxib treatment group, with the exception of patients with a ≥30% reduction from Baseline in the tanezumab 10 mg treatment group compared to the celecoxib treatment group.

- For the **change from Baseline in the BPI-sf scores**, in the BPI-sf Worst Pain score and BPI-sf Average Pain score, there was a decrease from Baseline (decrease = improvement) in all treatment groups at all weeks. The mean decrease from Baseline in both the BPI-sf Worst Pain score and BPI-sf Average Pain score was greater in patients in both tanezumab treatment groups than in patients in the celecoxib treatment group from Week 2 to Week 56 (Observed Data). At Week 16 and Week 56 (Multiple Imputation), patients in the tanezumab 5 mg treatment group showed greater mean decreases from Baseline in BPI-sf Worst Pain and Average Pain than patients in the celecoxib treatment group. Patients in the tanezumab 10 mg treatment group showed greater mean decreases from Baseline in BPI-sf Worst Pain and Average Pain than patients in the celecoxib treatment group at Week 16; at Week 56, the values for patients in the tanezumab 10 mg treatment group were similar to those in patients in the celecoxib treatment group.

  - For the BPI-sf Pain Interference Index, patients in the tanezumab treatment groups showed a larger mean decrease from Baseline than those in the celecoxib treatment group at all weeks from Week 2 to Week 64, except for the tanezumab 10 mg treatment group at Weeks 16 and 40 (Observed Data). At Weeks 16 and 56 (Multiple Imputation), patients in the tanezumab 5 mg treatment group showed a larger mean decrease from Baseline in the BPI-sf Pain Interference Index than patients in the

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tanezumab 10 mg treatment group and the celecoxib treatment group; the results for patients in the tanezumab 10 mg treatment group were similar to those for patients in the celecoxib treatment group.

- For the BPI-sf score of Pain Interference with General Activity, patients in the tanezumab treatment groups showed larger mean decreases from Baseline than patients in the celecoxib treatment group at all time points from Week 2 though Week 64 (Observed Data); at Weeks 16 and 56 (Multiple Imputation), the mean decrease from Baseline in patients in the tanezumab treatment groups was larger than in patients in the celecoxib treatment group.

- For the BPI-sf score of Pain Interference with Walking Ability, the mean decrease from Baseline in patients in the tanezumab 5 mg treatment group was larger than in patients in the celecoxib treatment group at all timepoints from Week 2 through Week 56; the mean decrease from Baseline in patients in the tanezumab 10 mg treatment group was larger than in patients in the celecoxib treatment group from Week 2 through Week 24 (Observed Data). At Weeks 16 and 56 (Multiple Imputation), the mean decrease from Baseline in patients in the tanezumab 5 mg treatment group was larger than in patients in the celecoxib treatment group; the results for patients in the tanezumab 10 mg treatment group were similar to those for patients in the celecoxib treatment group.

- For the BPI-sf score of Pain Interference with Sleep, patients in the tanezumab treatment groups showed a larger mean decrease from Baseline compared to patients in the celecoxib treatment group at all time points from Week 2 though Week 64, except for the tanezumab 10 mg treatment group at Week 40 (Observed Data). At Weeks 16 and 56 (Multiple Imputation), the mean decrease from Baseline in patients in the tanezumab treatment groups was larger than in patients in the celecoxib treatment group.

- For the BPI-sf score of Pain Interference with Normal Work, patients in the tanezumab treatment groups showed larger decreases from Baseline compared to patients in the celecoxib treatment group at all time points from Week 2 though Week 56, except for the tanezumab 5 mg treatment group at Week 2 and the tanezumab 10 mg treatment group at Weeks 4, 40, and 56 (Observed Data). At Weeks 16 and 56 (Multiple Imputation), the mean decrease from Baseline in patients in the tanezumab 5 mg treatment group was larger than in patients in the celecoxib treatment group; the results for patients in the tanezumab 10 mg treatment group were similar to those for patients in the celecoxib treatment group.

- Analysis of the **CLBP Responder Index** (composite endpoint of average LBPI score, PGA-LBP, and RMDQ score) showed higher proportions of responders in the tanezumab 5 mg treatment group than in the tanezumab 10 mg treatment group and the celecoxib treatment group at each week analyzed. At all weeks (Weeks 16, 24, 40, and 56), the

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proportion of responders was similar between the tanezumab 10 mg treatment group and the celecoxib treatment group (Mixed BOCF/LOCF).

- The proportion of patients showing a **≥2-point reduction from Baseline in the PGA-LBP** was larger in the tanezumab 5 mg treatment group than in the tanezumab 10 mg treatment group and the celecoxib treatment group at all timepoints (Weeks 16, 24, 40 and 56). The proportion of patients showing a ≥2-point reduction from Baseline in the PGA-LBP was larger in the tanezumab 10 mg treatment group than in the celecoxib treatment group at Weeks 24 and 40 (Mixed BOCF/LOCF).

- For each of the **Euro Quality of Life Health State Profile Dimensions** (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression), as well as for the Index Value, the mean values across treatment groups showed similar improvement from Baseline at Week 16 and Week 56.

- **WPAI:LBP change from Baseline**: At Weeks 16 and 56, mean decreases from Baseline (decrease = improvement) were observed for all WPAI:LBP measures, across all treatment groups. Patients in the tanezumab 5 mg treatment group showed a larger mean decrease from Baseline than those in the celecoxib treatment group in all measures at Weeks 16, 56, and 64, except for Percent Work Time Missed at Week 16, and Percent Impairment While Working at Week 64. Patients in the tanezumab 10 mg treatment group showed larger mean decreases from Baseline than those in the celecoxib treatment group for Percent Work Time Missed at Weeks 16, 56, and 64; in Percent Impairment While Working and in Percent Overall Work Impairment at Weeks 56 and 64. The mean decrease from Baseline for Percent Activity Impairment was similar between patients in the tanezumab 10 mg treatment group and the celecoxib treatment group at Weeks 16, 56, and 64.

- During the Treatment Period (ie, up to Week 56), the proportion of patients who **discontinued treatment due to insufficient clinical response** and the patient's meeting the protocol-specified pain criteria were similar in the tanezumab 10 mg treatment group (39 [41.9%]) and the celecoxib treatment group (36 [39.1%]); the tanezumab 5 mg treatment group (26 [28.3%]) had the lowest number of patients who discontinued for these reasons. For each comparison of a tanezumab treatment group versus the celecoxib treatment group, however, the 95% CI includes 0, so the difference between treatment groups in number of patients discontinuing is not significant. Four (4 [4.3%]) patients in the tanezumab 10 mg treatment group and one (1 [1.1%]) patient each in the tanezumab 5 mg treatment group and the celecoxib treatment group discontinued due to insufficient clinical response.

- At Baseline, the **incidence of rescue medication use per week** ranged from 31.2% to 39.1% across treatment groups and decreased in all treatment groups up to Week 16, to 16.3% to 28.3%. The incidence of use of rescue medication was lower in the tanezumab 5 mg treatment group than in the celecoxib treatment group at Weeks 12, 16, 32, 40, and

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56; at other weeks, the incidence of use of rescue medication in the tanezumab 5 mg treatment group was similar to or higher than that in the celecoxib treatment group. The incidence of use of rescue medication was lower in the tanezumab 10 mg treatment group than in the celecoxib treatment group from Week 1 through Week 32 and at Week 56; at Weeks 40 and 48, the incidence of use of rescue medication in the tanezumab 10 mg treatment group was similar to that in the celecoxib treatment group (LOCF).

The **mean number of days of rescue medication use per week** at Baseline ranged from 0.9 to 1.3 days and decreased at Week 16 to 0.5 to 0.7 days per week across the treatment groups. Up to Week 16, the number of days of rescue medication use across all treatment groups was small, mostly less than 1 day per week; from Week 24 through Week 56, the number of days of rescue medication use across all treatment groups ranged from 1.2 to 1.6 days per week. The mean number of days of rescue medication use was lower in the tanezumab treatment groups than in the celecoxib treatment group at all weeks from Week 1 though Week 56, except for Week 2 in the tanezumab 10 mg treatment group and Weeks 2 and 4 in the tanezumab 5 mg treatment group (LOCF).

- At Baseline, the **use of rescue medication per week** was less in patients in the tanezumab 10 mg treatment group (731 mg) compared to patients in the tanezumab 5 mg treatment group (1238 mg) or the celecoxib treatment group (1257 mg). Starting at Week 1 through Week 16, the mean amount of rescue medication used by patients in the tanezumab 5 mg treatment group and patients in the celecoxib treatment group was similar, except at Week 2 where rescue medication use in the tanezumab 5 mg treatment group was higher than in the celecoxib treatment group. Starting at Week 1 through Week 16, the mean amount of rescue medication used was lower in patients in the tanezumab 10 mg treatment group than in patients in the celecoxib treatment group (LOCF).

- **Treatment Satisfaction Measures**: At Week 16 and Week 56, most patients in all treatment groups said that they were ‘Very Satisfied’, ‘Satisfied’, or "Somewhat Satisfied' with the ability of the study medication to prevent/treat their condition and the way the study medication relieved their symptoms. Over 93% of patients in all treatment groups reported at Weeks 16 and 56 that they experienced no side effects from the study medication.

- In general, most of patients in all treatment groups expressed a preference for the study drug received compared to previous treatment, and a willingness to use the study medication received for low back pain, in each **mPRTI** endpoint at Weeks 16 and 56.

**Pharmacokinetic Results**

The mean tanezumab plasma concentrations were higher in the tanezumab 10 mg treatment group than the tanezumab 5 mg treatment group at all nominal sampling times (Week 2 to Week 56) in a dose-proportional manner. By Week 64, 16 weeks after the seventh dose of study medication, the mean tanezumab plasma concentrations were 5.7% and 14.9% of the

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mean Week 48 trough concentrations for the tanezumab 5 mg and tanezumab 10 mg treatment groups, respectively.

### Pharmacodynamic Results

Blood samples were analyzed for the determination of serum concentration of soluble p75, total NGF, and proNGF.

Mean and median serum soluble p75 concentrations were comparable at all time points for all treatment groups, suggesting the presence of tanezumab does not affect levels of circulating soluble p75.

Mean serum total NGF concentrations were comparable at Baseline across treatment groups and increased with tanezumab dosing. Mean total NGF trough concentrations were higher in the tanezumab 10 mg treatment group compared with the tanezumab 5 mg treatment group at all time points. Mean serum proNGF was comparable across treatment groups at all nominal sampling times.

### Safety Results

At least one treatment-emergent AE was experienced by 58 (63.0%), 51 (54.8%), and 62 (67.4%) patients in the tanezumab 5 mg treatment group, the tanezumab 10 mg treatment group, and the celecoxib treatment group, respectively; 4 (4.3%), 9 (9.7%), and 2 (2.2%) patients in the tanezumab 5 mg treatment group, the tanezumab 10 mg treatment group, and the celecoxib treatment group, respectively, experienced at least one treatment-emergent SAE (Table S3). Most treatment-emergent AEs were mild or moderate in severity.

There were 3 (3.3%), 5 (5.4%), and 4 (4.3%) patients in the tanezumab 5 mg treatment group, the tanezumab 10 mg treatment group, and the celecoxib treatment group, respectively, that discontinued study medication due to AEs. Most patients continued in the study after discontinuation of study medication due to AEs. Few patients had a dose reduction or temporary discontinuation during the study (Table S3). Most treatment-emergent AEs were considered by the Investigator not to be related to study medication.

**Table S3. Treatment-Emergent Adverse Events (All-Causality) During the Treatment Period**

| Number (%) of Subjects | Tanezumab 5 mg n (%) | Tanezumab 10 mg n (%) | Celecoxib n (%) |
|---|---|---|---|
| Subjects evaluable for adverse events | 92 | 93 | 92 |
| Number of adverse events | 155 | 110 | 123 |
| Subjects with adverse events | 58 (63.0) | 51 (54.8) | 62 (67.4) |

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### Table S3. Treatment-Emergent Adverse Events (All-Causality) During the Treatment Period

| Number (%) of Subjects | Tanezumab 5 mg n (%) | Tanezumab 10 mg n (%) | Celecoxib n (%) |
|---|---|---|---|
| Subjects with serious adverse events | 4 (4.3) | 9 (9.7) | 2 (2.2) |
| Subjects with severe adverse events | 3 (3.3) | 2 (2.2) | 1 (1.1) |
| Subjects discontinued study drug due to adverse event | 3 (3.3) | 5 (5.4) | 4 (4.3) |
| Subjects discontinued from study due to adverse event (a) | 1 (1.1) | 1 (1.1) | 0 |
| Subjects discontinued study drug due to adverse event and continued Study (b) | 2 (2.2) | 4 (4.3) | 4 (4.3) |
| Subjects with dose reduced or temporary discontinuation due to adverse events | 2 (2.2) | 1 (1.1) | 0 |

Includes treatment-emergent events that begin up to the week 56 (end of treatment) visit date for subjects who completed the treatment period or up
to the withdrawal from treatment date for subjects who withdrew early from the treatment period.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the subject
to be discontinued from study
MedDRA v22.0 coding dictionary applied.
CCI [redacted]

During the 24-week Safety Follow-up Period and Early Termination Follow-up Period, a higher percentage of patients in the tanezumab 5 mg treatment group (47.3%) reported AEs than those in the tanezumab 10 mg treatment group (40.2%) or the celecoxib treatment group (40.4%). During this period, few SAEs were reported in all treatment groups (Table S4).

### Table S4. Treatment-Emergent Adverse Events (All-Causality) During the Follow-up Period

| Number (%) of Subjects | Tanezumab 5 mg n (%) | Tanezumab 10 mg n (%) | Celecoxib n (%) |
|---|---|---|---|
| Subjects evaluable for adverse events | 91 | 87 | 89 |
| Number of adverse events | 85 | 53 | 62 |
| Subjects with adverse events | 43 (47.3) | 35 (40.2) | 36 (40.4) |

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**Table S4. Treatment-Emergent Adverse Events (All-Causality) During the Follow-up Period**

| Number (%) of Subjects | Tanezumab 5 mg n (%) | Tanezumab 10 mg n (%) | Celecoxib n (%) |
|---|---|---|---|
| Subjects with serious adverse events | 5 (5.5) | 2 (2.3) | 2 (2.2) |
| Subjects with severe adverse events | 0 | 0 | 1 (1.1) |
| Subjects discontinued study drug due to adverse event | 0 | 0 | 0 |
| Subjects discontinued from study due to adverse event (a) | 0 | 0 | 0 |
| Subjects discontinued study drug due to adverse event and continued Study (b) | 0 | 0 | 0 |
| Subjects with dose reduced or temporary discontinuation due to adverse events | 0 | 0 | 0 |

Includes treatment-emergent events that begin after the week 56 (end of treatment) visit date for subjects who completed the treatment period
or after the withdrawal from treatment date for subjects who withdrew early from the treatment period.
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
(a) Subjects who have an AE record that indicates that the AE caused the subject to be discontinued from the study
(b) Subjects who have an AE record that indicates that action taken with study treatment was drug withdrawn but AE did not cause the Subject to be
discontinued from study
MedDRA v22.0 coding dictionary applied.
CCI [redacted]

Of the treatment-emergent AEs that occurred most frequently (≥2% in any treatment group) during the Treatment Period (Table S5), Nasopharyngitis, Fall, Arthralgia, Contusion, Hypoaesthesia, and Back pain were the most commonly reported AEs in one or both of the tanezumab treatment groups, and were mostly reported in a similar number of patients compared to the celecoxib treatment group; the exception was Nasopharyngitis which was reported in more patients in the tanezumab treatment groups.

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**Table S5. Incidence of Treatment-Emergent Adverse Events Occurring in ≥2% Patients During the Treatment Period by Descending Frequency (All-Causality)**

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=92) | Tanezumab 10 mg (N=93) | Celecoxib (N=92) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Nasopharyngitis | 14 (15.2) | 13 (14.0) | 6 (6.5) |
| Back pain | 4 (4.3) | 5 (5.4) | 4 (4.3) |
| Contusion | 3 (3.3) | 4 (4.3) | 2 (2.2) |
| Fall | 6 (6.5) | 4 (4.3) | 3 (3.3) |
| Arthralgia | 5 (5.4) | 3 (3.2) | 6 (6.5) |
| Headache | 2 (2.2) | 3 (3.2) | 2 (2.2) |
| Intervertebral disc protrusion | 2 (2.2) | 3 (3.2) | 3 (3.3) |
| Carpal tunnel syndrome | 1 (1.1) | 2 (2.2) | 0 |
| Dental caries | 2 (2.2) | 2 (2.2) | 2 (2.2) |
| Dysmenorrhoea | 1 (1.1) | 2 (2.2) | 0 |
| Eczema | 0 | 2 (2.2) | 0 |
| Hypoaesthesia | 5 (5.4) | 2 (2.2) | 3 (3.3) |
| Influenza | 1 (1.1) | 2 (2.2) | 2 (2.2) |
| Musculoskeletal stiffness | 1 (1.1) | 2 (2.2) | 2 (2.2) |
| Orthostatic hypotension | 0 | 2 (2.2) | 1 (1.1) |
| Rotator cuff syndrome | 0 | 2 (2.2) | 0 |
| Sudden hearing loss | 0 | 2 (2.2) | 0 |
| Diarrhoea | 1 (1.1) | 1 (1.1) | 3 (3.3) |
| Dizziness | 2 (2.2) | 1 (1.1) | 2 (2.2) |
| Epicondylitis | 0 | 1 (1.1) | 2 (2.2) |
| Gastroenteritis | 1 (1.1) | 1 (1.1) | 3 (3.3) |
| Ligament sprain | 2 (2.2) | 1 (1.1) | 2 (2.2) |
| Muscle spasms | 2 (2.2) | 1 (1.1) | 0 |
| Myalgia | 3 (3.3) | 1 (1.1) | 1 (1.1) |
| Pain in extremity | 3 (3.3) | 1 (1.1) | 3 (3.3) |
| Pharyngitis | 2 (2.2) | 1 (1.1) | 1 (1.1) |
| Pyrexia | 2 (2.2) | 1 (1.1) | 4 (4.3) |
| Tendon rupture | 2 (2.2) | 1 (1.1) | 0 |
| Tendonitis | 0 | 1 (1.1) | 2 (2.2) |
| Arthropod sting | 2 (2.2) | 0 | 0 |
| Asthma | 2 (2.2) | 0 | 0 |
| Bradycardia | 2 (2.2) | 0 | 1 (1.1) |
| Cervical radiculopathy | 2 (2.2) | 0 | 0 |
| Cough | 2 (2.2) | 0 | 0 |

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**Table S5. Incidence of Treatment-Emergent Adverse Events Occurring in ≥2% Patients During the Treatment Period by Descending Frequency (All-Causality)**

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=92) | Tanezumab 10 mg (N=93) | Celecoxib (N=92) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Dyslipidaemia | 2 (2.2) | 0 | 0 |
| Dysuria | 2 (2.2) | 0 | 0 |
| Fatigue | 2 (2.2) | 0 | 1 (1.1) |
| Hypertension | 2 (2.2) | 0 | 3 (3.3) |
| Hyperventilation | 0 | 0 | 2 (2.2) |
| Joint effusion | 2 (2.2) | 0 | 0 |
| Meniscus injury | 2 (2.2) | 0 | 0 |
| Muscle strain | 0 | 0 | 2 (2.2) |
| Musculoskeletal pain | 3 (3.3) | 0 | 3 (3.3) |
| Palpitations | 0 | 0 | 2 (2.2) |
| Periarthritis | 2 (2.2) | 0 | 0 |
| Pneumonia | 3 (3.3) | 0 | 1 (1.1) |
| Rash | 2 (2.2) | 0 | 1 (1.1) |
| Rhinitis allergic | 2 (2.2) | 0 | 0 |
| Somnolence | 1 (1.1) | 0 | 2 (2.2) |
| Stomatitis | 2 (2.2) | 0 | 0 |
| Upper respiratory tract inflammation | 0 | 0 | 2 (2.2) |

Includes treatment-emergent events that begin up to the week 56 (end of treatment) visit date for subjects who completed the treatment period or up to the
withdrawal from treatment date for subjects who withdrew early from the treatment period.
Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
MedDRA v22.0 coding dictionary applied.
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Nasopharyngitis was the most frequently reported AE across treatment groups during the 24-week Safety Follow-up or Early Termination Follow-up Period, and it was reported with similar frequency across treatment groups. Arthralgia and Periarthritis were reported in more patients in the tanezumab treatment groups than in the celecoxib treatment group, and Back pain was reported in more patients in the celecoxib treatment group than in the tanezumab treatment groups. Other AEs were reported in too few patients to draw conclusions (Table S6).

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**Table S6. Incidence of Treatment-Emergent Adverse Events During the Safety Follow-up Period (All Causalities) - Safety Population**

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=91) | Tanezumab 10 mg (N=87) | Celecoxib (N=89) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Nasopharyngitis | 8 (8.8) | 8 (9.2) | 8 (9.0) |
| Arthritis | 0 | 3 (3.4) | 0 |
| Constipation | 0 | 3 (3.4) | 1 (1.1) |
| Arthralgia | 6 (6.6) | 2 (2.3) | 1 (1.1) |
| Back pain | 3 (3.3) | 2 (2.3) | 5 (5.6) |
| Fall | 1 (1.1) | 2 (2.3) | 2 (2.2) |
| Ligament sprain | 1 (1.1) | 2 (2.3) | 2 (2.2) |
| Tenosynovitis | 0 | 2 (2.3) | 2 (2.2) |
| Atrioventricular block | 0 | 1 (1.1) | 0 |
| Bronchitis | 0 | 1 (1.1) | 0 |
| Cellulitis | 0 | 1 (1.1) | 0 |
| Conjunctivitis allergic | 0 | 1 (1.1) | 0 |
| Contusion | 2 (2.2) | 1 (1.1) | 1 (1.1) |
| Dyslipidaemia | 0 | 1 (1.1) | 0 |
| Eczema | 0 | 1 (1.1) | 0 |
| Haemangioma | 0 | 1 (1.1) | 0 |
| Headache | 2 (2.2) | 1 (1.1) | 2 (2.2) |
| Hepatic function abnormal | 0 | 1 (1.1) | 0 |
| Hordeolum | 0 | 1 (1.1) | 0 |
| Hyperlipidaemia | 0 | 1 (1.1) | 0 |
| Hypoaesthesia | 1 (1.1) | 1 (1.1) | 2 (2.2) |
| Hypotension | 0 | 1 (1.1) | 0 |
| Influenza | 0 | 1 (1.1) | 0 |
| Insomnia | 1 (1.1) | 1 (1.1) | 1 (1.1) |
| Liver function test abnormal | 0 | 1 (1.1) | 0 |
| Musculoskeletal pain | 0 | 1 (1.1) | 1 (1.1) |
| Oesophageal carcinoma | 0 | 1 (1.1) | 0 |
| Osteoarthritis | 0 | 1 (1.1) | 0 |
| Pain in extremity | 2 (2.2) | 1 (1.1) | 1 (1.1) |
| Periarthritis | 4 (4.4) | 1 (1.1) | 0 |
| Procedural pain | 0 | 1 (1.1) | 0 |
| Pyrexia | 0 | 1 (1.1) | 1 (1.1) |
| Road traffic accident | 0 | 1 (1.1) | 0 |

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### Table S6. Incidence of Treatment-Emergent Adverse Events During the Safety Follow-up Period (All Causalities) - Safety Population

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=91) | Tanezumab 10 mg (N=87) | Celecoxib (N=89) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Sinusitis | 0 | 1 (1.1) | 0 |
| Somnolence | 1 (1.1) | 1 (1.1) | 0 |
| Syncope | 0 | 1 (1.1) | 0 |
| Tonsillitis | 0 | 1 (1.1) | 0 |
| Abdominal discomfort | 0 | 0 | 1 (1.1) |
| Abdominal pain upper | 1 (1.1) | 0 | 1 (1.1) |
| Actinic keratosis | 1 (1.1) | 0 | 0 |
| Anastomotic ulcer | 1 (1.1) | 0 | 0 |
| Arthropathy | 1 (1.1) | 0 | 0 |
| Basedow's disease | 1 (1.1) | 0 | 0 |
| Blood creatine phosphokinase increased | 2 (2.2) | 0 | 0 |
| Bone neoplasm | 1 (1.1) | 0 | 0 |
| Bradycardia | 0 | 0 | 1 (1.1) |
| Calcinosis | 1 (1.1) | 0 | 0 |
| Cardiac failure | 1 (1.1) | 0 | 0 |
| Chalazion | 1 (1.1) | 0 | 0 |
| Chondrocalcinosis pyrophosphate | 0 | 0 | 1 (1.1) |
| Chronic kidney disease | 1 (1.1) | 0 | 0 |
| Decreased appetite | 1 (1.1) | 0 | 1 (1.1) |
| Dental caries | 1 (1.1) | 0 | 0 |
| Dental cyst | 0 | 0 | 1 (1.1) |
| Depression | 0 | 0 | 1 (1.1) |
| Diabetes mellitus | 0 | 0 | 1 (1.1) |
| Diarrhoea | 1 (1.1) | 0 | 0 |
| Dizziness | 0 | 0 | 2 (2.2) |
| Dizziness postural | 0 | 0 | 1 (1.1) |
| Dry skin | 0 | 0 | 1 (1.1) |
| Epicondylitis | 2 (2.2) | 0 | 0 |
| Extrasystoles | 0 | 0 | 1 (1.1) |
| Femoroacetabular impingement | 0 | 0 | 1 (1.1) |
| Gallbladder polyp | 0 | 0 | 1 (1.1) |
| Gastritis | 1 (1.1) | 0 | 0 |
| Gastroenteritis | 1 (1.1) | 0 | 0 |
| Haemorrhoids | 1 (1.1) | 0 | 0 |
| Hand fracture | 1 (1.1) | 0 | 0 |

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### Table S6. Incidence of Treatment-Emergent Adverse Events During the Safety Follow-up Period (All Causalities) - Safety Population

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=91) | Tanezumab 10 mg (N=87) | Celecoxib (N=89) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Hyperkeratosis | 1 (1.1) | 0 | 0 |
| Hypertension | 0 | 0 | 1 (1.1) |
| Hyperuricaemia | 0 | 0 | 1 (1.1) |
| Hypogeusia | 1 (1.1) | 0 | 0 |
| Joint effusion | 2 (2.2) | 0 | 0 |
| Large intestine polyp | 1 (1.1) | 0 | 0 |
| Limb discomfort | 1 (1.1) | 0 | 0 |
| Lipoma | 1 (1.1) | 0 | 0 |
| Malaise | 1 (1.1) | 0 | 0 |
| Musculoskeletal stiffness | 1 (1.1) | 0 | 0 |
| Nail injury | 1 (1.1) | 0 | 0 |
| Nausea | 1 (1.1) | 0 | 1 (1.1) |
| Neck pain | 1 (1.1) | 0 | 0 |
| Nephrolithiasis | 0 | 0 | 1 (1.1) |
| Oropharyngeal pain | 1 (1.1) | 0 | 0 |
| Orthostatic hypotension | 1 (1.1) | 0 | 0 |
| Osteonecrosis | 1 (1.1) | 0 | 0 |
| Pruritus | 1 (1.1) | 0 | 0 |
| Pseudomonas infection | 0 | 0 | 1 (1.1) |
| Pyelonephritis acute | 1 (1.1) | 0 | 0 |
| Rapidly progressive osteoarthritis | 1 (1.1) | 0 | 0 |
| Rash | 1 (1.1) | 0 | 2 (2.2) |
| Renal abscess | 1 (1.1) | 0 | 0 |
| Renal neoplasm | 0 | 0 | 1 (1.1) |
| Rhinorrhoea | 1 (1.1) | 0 | 0 |
| Rotator cuff syndrome | 1 (1.1) | 0 | 1 (1.1) |
| Sciatica | 0 | 0 | 1 (1.1) |
| Sinus tachycardia | 0 | 0 | 1 (1.1) |
| Skin abrasion | 0 | 0 | 1 (1.1) |
| Spinal compression fracture | 0 | 0 | 1 (1.1) |
| Temporomandibular joint syndrome | 1 (1.1) | 0 | 0 |
| Tendonitis | 2 (2.2) | 0 | 0 |
| Tinnitus | 1 (1.1) | 0 | 0 |
| Toothache | 1 (1.1) | 0 | 0 |
| Trigeminal neuralgia | 1 (1.1) | 0 | 0 |

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**Table S6. Incidence of Treatment-Emergent Adverse Events During the Safety Follow-up Period (All Causalities) - Safety Population**

| Number of Subjects Evaluable for AEs | Tanezumab 5 mg (N=91) | Tanezumab 10 mg (N=87) | Celecoxib (N=89) |
|---|---|---|---|
| **Number (%) of Subjects: by Preferred Term** | **n (%)** | **n (%)** | **n (%)** |
| Trigger finger | 1 (1.1) | 0 | 0 |
| Ureterolithiasis | 1 (1.1) | 0 | 1 (1.1) |
| Urticaria | 0 | 0 | 2 (2.2) |
| Vision blurred | 1 (1.1) | 0 | 0 |
| White blood cell count increased | 1 (1.1) | 0 | 0 |
| Wound complication | 0 | 0 | 1 (1.1) |

Includes treatment-emergent events that begin after the week 56 (end of treatment) visit date for subjects who completed the treatment period or
after the withdrawal from treatment date for subjects who withdrew early from the treatment period.
Subjects are only counted once per treatment per event.
Adverse events are shown by descending frequency by the highest tanezumab dose.
MedDRA v22.0 coding dictionary applied.
CCI [redacted]

- **Treatment-Related Adverse Events:** During the Treatment Period, at least one treatment-related AE was experienced by 10 (10.9%), 6 (6.5%) and 12 (13.0%) patients in the tanezumab 5 mg treatment group, the tanezumab 10 mg treatment group, and the celecoxib treatment group, respectively; 1 (1.1%) patient, in the tanezumab 10 mg treatment group, experienced a treatment-related SAE.

- **Severe Adverse Events:** The only treatment-related severe AE during the Treatment Period was Osteonecrosis, reported in one patient in the tanezumab 10 mg treatment group (which was adjudicated to a diagnosis of Rapidly progressive OA type 2); this was also an SAE. Study medication was withdrawn, the patient had a TJR, recovered, and transitioned to the substudy.

- **Injection Site Reactions:** Injection site reactions were reported in one patient, in the tanezumab 5 mg treatment group. This patient had injection site discoloration and injection site pruritus when study medication was administered on study Day 1 and 61, and injection site pruritus on study day 117; all reactions were mild in severity. These events were considered by the Investigator to be related to study medication. The patient also received study medication on study days 167, 229, 282, and 334 with no additional injection site reactions reported.

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- **Potential Hypersensitivity Adverse Events:** Overall few potential hypersensitivity adverse events were reported during the study: eight AEs in 6 (6.5%) patients in the tanezumab 5 mg treatment group, and six AEs in 4 (4.3%) patients in the tanezumab 10 mg treatment group. All potential hypersensitivity AEs were mild in severity and none were considered by the Investigator to be related to study medication.

- **Tier 1 Adverse Events:** A pre-specified composite of AEs of potential sympathetic dysfunction (Syncope, Bradycardia, Orthostatic hypertension, Anhidrosis, and Hypohidrosis) was considered clinically important and classified as a Tier 1 AE in the product's Safety Review Plan. AEs within the Tier 1 composite were infrequently reported with a similar incidence across treatment groups. The composite Tier 1 AE incidence was the same (2.2%) across all treatment groups

- **Tier 2 Adverse Events:** Tier 2 AEs were defined as AEs occurring in ≥3% of patients in any treatment group; the frequency of occurrence in each tanezumab treatment group was compared to celecoxib, with 95% CIs provided to help gauge the precision of the estimates for risk difference. There were no differences in the frequency of occurrence of Tier 2 AEs (all 95 % CIs included 0) in either tanezumab treatment group compared to the celecoxib treatment group

- **Deaths:** No patients died during the study.

- **Serious Adverse Events:** During the Treatment Period, SAEs were infrequently reported in all treatment groups; the only SAE that occurred in more than one patient in a treatment group was Rotator cuff syndrome, which occurred in two patients in the tanezumab 10 mg treatment group. Of the 15 SAEs, one was considered by the Investigator to be related to study medication: Osteonecrosis (left femoral head), severe in intensity, in the tanezumab 10 mg treatment group (which was adjudicated to a diagnosis of Rapidly progressive OA type 2).

  During the 24-week Safety Follow-up or Early Termination Follow-up Periods, nine patients had SAEs: 5 (5.5%) in the tanezumab 5 mg treatment group, 2 (2.3%) in the tanezumab 10 mg treatment group, and 2 (2.2%) in the celecoxib treatment group. No individual preferred term was reported in more than one patient. Of the nine SAEs, one, Rapidly progressive OA (right knee), moderate in severity, in the tanezumab 5 mg treatment group, was considered by the Investigator to be related to study medication.

- **Adverse Events of Abnormal Peripheral Sensation:** The most frequently reported AE of abnormal peripheral sensation during the Treatment Period was Hypoesthesia, reported in 5 (5.4%) patients in the tanezumab 5 mg treatment group, 2 (2.2%) patients in the tanezumab 10 mg treatment group, and 3 (3.3%) patients in the celecoxib treatment group. All AEs of abnormal peripheral sensation during the Treatment Period were mild in severity, except for a single event of Sciatica in a patient in the celecoxib treatment group, which was moderate in severity.

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- **Peripheral Neurological Consultation:** Three patients each in the tanezumab 5 mg treatment group and the celecoxib treatment group had AEs of abnormal peripheral sensation that met criteria for requiring a neurologic consultation; no patient in the tanezumab 10 mg treatment group had an AE of abnormal peripheral sensation that met criteria for requiring a neurologic consultation. Clinical data, including consultation data when available, were reviewed by an external neurology expert for all patients who had at least one event requiring consultation. The most frequent expert primary diagnoses were mononeuropathy and radiculopathy; there was no dose-dependence in the occurrence. Mononeuropathy (Carpal tunnel syndrome [CTS]) was diagnosed in two patients in the tanezumab 5 mg treatment group; in both cases the diagnosis was definitive, new, and the presentation was sensory. In one patient, the CTS was bilateral and in the other patient, it was on the right side. Radiculopathy was diagnosed in one patient in the tanezumab 5 mg treatment group (possible, cervical, new, sensory, right-sided) and in two patients in the celecoxib treatment group (both: probable, lumbosacral, pre-existing, sensory, left-sided). Polyneuropathy was diagnosed in one patient, in the celecoxib treatment group (possible, length-dependent, new, sensory, bilateral).

- **Adverse Events of Possible Decreased Sympathetic Function:** AEs indicative of possible decreased sympathetic function were reported infrequently in all treatment groups with no individual AE being reported in more than two patients in the tanezumab treatment groups. All AEs of possible decreased sympathetic function were mild, except for one event of Diarrhea in the celecoxib treatment group which was moderate in severity

- **Consultations for Adverse Events of Possible Decreased Sympathetic Function:** The only key AEs meeting criteria for consultation were OH, Bradycardia and Syncope. No patient was reported to have Anhidrosis or Hypohidrosis. Consultations were obtained for all patients who met the criteria for a consultation. Sympathetic neuropathy was not confirmed for any of the patients who had a consultation, as determined by the Investigator after a review of clinical data including available consultation material.

- **Neuropathy Impairment Score:** The conclusion from the neurological examination for over 97% of patients across all treatment groups was that there was no new or worsened neurological examination abnormality at the last assessment. Less than 2% of patients in any treatment group had a new or worsened neurological examination abnormality that was considered by the Investigator to be clinically significant.

- **Adjudication:** The adjudicated outcomes of the six potential joint safety events analyzed by the Adjudication Committee were Rapidly progressive OA type 1 (right/left knee, one patient [2 events]) and Other: Pre-existing Subchondral insufficiency fracture, in the tanezumab 5 mg treatment group; Rapidly progressive OA type 2 (SAE of Osteonecrosis) and Subchondral insufficiency fracture, in the tanezumab 10 mg treatment group; and Other: Pre-existing arthroplasty, in the celecoxib treatment group. Primary osteonecrosis and Pathological fracture were not adjudicated outcomes in this study.

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One patient, in the tanezumab 5 mg treatment group, had two joint safety events adjudicated as Rapidly progressive OA type 1, one in each knee. The joints had radiographic evidence of OA on the Screening X-ray (KL grade 1 or 2); the patient did not have a TJR. One patient, in the tanezumab 10 mg treatment group, had a joint safety event adjudicated as Rapidly progressive OA type 2. The affected joint was a hip that had radiographic evidence of OA on the Screening X-ray (KL grade 1); the patient had a TJR. One patient, in the tanezumab 10 mg treatment group, had an adjudicated outcome of Subchondral insufficiency fracture; the affected joint was a knee that had a KL grade of 2 on the Screening X-ray. One patient, in the tanezumab 5 mg treatment group, had an adjudicated outcome of Other: Pre-existing Subchondral insufficiency fracture; the affected joint was a knee that had a KL grade of 1 on the Screening X-ray. One patient, in the celecoxib treatment group, had an adjudicated outcome of Other: pre-existing arthroplasty; the affected joint was a knee that had a KL grade N/A on the screening X-ray.

- **Total Joint Replacements:** One patient, in the tanezumab 10 mg treatment group, who had an adjudicated outcome of Rapidly progressive OA type 2, had a hip TJR during the study. The patient agreed to participate in the TJR substudy.

- **Laboratory Parameters:** The incidence of patients with normal Baseline who had post-Baseline laboratory test abnormalities that met the pre-specified threshold for change from Baseline was low, mostly affected one or two patients within a treatment group and was mostly evenly distributed across treatment groups. Laboratory abnormalities considered clinically significant by the Investigator post-Baseline were to be reported as AEs. All laboratory abnormalities reported as AEs in the Treatment Period were reported in one patient each.

- **Vital Signs:** Categorical changes from Baseline to the last post-Baseline value in sitting BP during the Treatment Period (ie, up to Week 56) were mostly similar across treatment groups for systolic and diastolic BP, except for the sitting systolic and diastolic BP of >0 to <10, where a higher proportion of the celecoxib treatment group showed a change compared to the tanezumab 5 mg treatment group and tanezumab 10 mg treatment group. Overall, there was no dose-dependency in the differences between treatment groups. Categorical changes in sitting systolic and diastolic BP with a maximum increase from Baseline were mostly similar across the treatment groups, except for the increase in sitting systolic BP of >10 to 20 and sitting diastolic BP of >0 to 10, where a higher proportion of the tanezumab 5 mg treatment group showed an increase compared to the tanezumab 10 mg treatment group and celecoxib treatment group. Overall, there was no dose-dependency in the differences between treatment groups. Categorical changes in sitting systolic and diastolic BP with a maximum decrease from Baseline were mostly similar across the treatment groups. Overall, there was no dose-dependency in the differences between treatment groups.

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AEs associated with abnormal vital signs during the Treatment Period were infrequently observed across treatment groups.

- **ECG:** One patient, in the tanezumab 10 mg treatment group, had a QTc corrected using Bazett's formula (QTcB)/QTc corrected using Fridericia's formula (QTcF) value ≥500 msec at any point during the study. This patient had a QTcB and QTcF value ≥500 msec at Screening. The maximum changes in all ECG parameters up to the End of Study were similar across treatment groups.

- **Immunogenicity:** Treatment-emergent (TE) ADA status (ie, TE ADA+ or TE ADA-) did not appear to influence the proportion of patients identified as responders (ie, patients with a reduction from Baseline in average LBPI score of ≥30% at Week 16) in the tanezumab treatment groups. The overall percent incidence of AEs in the combined TE ADA+ tanezumab treatment group was comparable to the corresponding TE ADA- combined tanezumab treatment group.

### CONCLUSIONS

The primary objective of this study was to evaluate the long-term safety of treatment with tanezumab. Although the study was not powered nor designed to detect treatment differences in efficacy,

- Patients treated with tanezumab 5 mg had a greater mean change from Baseline in the LBPI score and PGA-LBP compared with patients treated with celecoxib at Week 16 and 56. Patients treated with tanezumab 5 mg had a greater mean change from Baseline in the RMDQ score than patients treated with celecoxib at Week 56, but not at Week 16.

- Patients treated with tanezumab 10 mg had a greater mean change from Baseline in the LBPI and RMDQ scores compared to patients treated with celecoxib at Week 16; results for tanezumab 10 mg and celecoxib treatment were similar for the LBPI and RMDQ scores at Week 56 and for the PGA-LBP at Weeks 16 and 56.

- Tanezumab treatment was generally safe and well-tolerated in Japanese patients with CLBP in this study. The adverse event data were generally consistent with previous tanezumab CLBP studies and no new safety signals were identified.

- Three patients contributed to the composite joint safety endpoint: one patient in the tanezumab 5 mg treatment group with an adjudicated diagnosis of Rapidly progressive OA type 1; in the tanezumab 10 mg treatment group, one patient each had an adjudicated diagnosis of Rapidly progressive OA type 2 and Subchondral insufficiency fracture. The patient with Rapidly progressive OA type 2 had a TJR.

- The adverse event data related to abnormal peripheral sensation were consistent with previous studies and the incidence of these adverse events was higher in the

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tanezumab 5 mg treatment group than in the tanezumab 10 mg treatment group and the celecoxib treatment group.

- There was no evidence of an effect of tanezumab on sympathetic nervous system function.
- There was no evidence of an effect of tanezumab on safety related to vital signs, ECG measures, or safety laboratory tests.
- The immunogenicity results do not provide any evidence that the presence of treatment-emergent ADA affects the safety or efficacy profile of tanezumab.